# Opciones de "Primera línea" en Terapia Antirretroviral: ¿Cuál escoger?
# (Selecting the Initial Antiretroviral Regimen for the Treatment of HIV Disease)

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The first effective antiretroviral drug, zidovudine, was introduced in 1986 but it was in 1996, with the introduction of protease inhibitors and combination regimens, that the age of effective therapy truly began. It was about the same time, in 1996, that quantitative HIV-1 assays became available. Thus, physicians were equipped with drugs to control HIV, improve immune dysfunction and maintain or restore the health of patients with advanced HIV infection. There are now fourteen drugs available and multiple combinations which might be used. Combinations of 3 or more drugs are recommended to assure maximal suppression and a durable response. It is conceivable that a two drug or even a single drug regimen might achieve the same results but none of the currently available agents can do so.

## Initiation of Treatment

The first decision may be when to start. The initiation of therapy depends first and foremost upon the patient. The patient must be educated about the risks and benefits, the need for strict compliance, the rigors and costs of the medications and the monitoring that HAART requires. There are a number of opinions about starting, and they are not all in agreement. And they change with advances in our knowledge base. Currently, most experts would agree that any patient with AIDS should be treated, regardless of the HIV RNA or CD4 count. Also, there is a consensus that anyone with HIV RNA of > 10,000 copies/ml (by the branched DNA assay) or > 20,000 copies/ml by the RT-PCR assay AND less than 500 CD4 cells is a candidate for treatment. With CD4 cell counts over 500 cells/ml, some experts recommend treatment if the HIV RNA is elevated, whereas others will delay and monitor the patient. Also, for patients with CD4 counts between 200 and 500, there is a difference of opinion regarding treatment: some recommend treatment if the HIV RNA load is > 5000 copies /ml (or 10,000 copies by RT-PCR), others do not. There is data which demonstrates better response to treatment if the CD4 count is > 350 cells than if it is < 350 cells/ml. There is also some controversy over initiating treatment for persons with the Acute Retroviral Syndrome. Data now available to us does not answer the key questions regarding long term benefit of starting HAART so early in the course of the disease. Whereas suppression of HIV replication is greater than is achieved in advanced HIV infection, the specter of long term toxicity is of concern.

## Choice of the Initial Regimen

The options for treatment continue to expand, but we have only a general sense of which are the most potent, which produce the most durable response and which are the safest. For example, saquinavir, because of poor bioavailability is generally less potent than other PIs. The NNRTIs are all potent drugs, with efavirenz producing greater decreases in viral load than the other two, and maintaining activity against some strains resistant to other NNRTIs. Toxicity varies considerably. Ritonavir in full doses of 600 mg bid produces GI intolerance in many patients, whereas the other PIs cause less severe GI intolerance. Nelfinavir is noted to cause loose bowel movements or diarrhea in many recipients, and indinavir is associated with renal colic in some patients. Among the NNRTIs, nevirapine may cause a severe dermatitis, whereas efavirenz and delavirdine do not – or at not such severe dermatitis. Efavirenz, on the other hand, causes some CNS symptoms in 50% of recipients. The abnormalities of long term HAART, the lipodystropy or fat redistribution syndrome and hyperlipidemias seem to occur at a lower frequency with NNRTI containing regimens than do those containing PIs. Recommended options are listed in the table below. One drug or combination from column A and one combination from column B are chosen to formulate a HAART regimen.

**Recommended Antiretroviral Regimens for Initial Treatment: One selection from Each Column**

| **Column A** | **Column B** |
|---|---|
| Amprenavir | Zidovudine + Didanosine |
| Indinavir | Stavudine + Didanosine |
| Nelfinavir | Zidovudine +Zalcitabine |
| Ritonavir | Stavudine + Lamivudine |
| Saquinavir-SGC | Zidovudine + Lamivudine |
| Ritonavir + Saquinavir-SGC | Didanosine + Lamivudine |
| Indinavir & Ritonavir | |
| Delavirdine | |
| Efavirenz | |
| Nevirapine | |

A PI-based regimen with two NRTIs has the proven to be potent and with excellent durability lasting for more than three years, but there is data to suggest that a NNRTI combined with two NRTIs may be equally potent. There is also data to suggest that the combination of didanosine and lamivudine is more effective than zidovudine and lamivudine. Abacavir may be substituted for one of the drugs in column A but it seems to be less effective for patients with HIV RNA copies of > 100,000/ml. Also, its potential to produce a fatal hypersensitivity reaction which at the onset cannot be distinguished from respiratory tract infections or other febrile illnesses make this a problematic drug to use. In my opinion, abacavir should probably be reserved for salvage regimens and not used in initial regimens.

Perhaps the greatest determinate of a successful regimen will be the one to which the patient can adhere. For this reason, regimens which require the patient to take medication twice a day rather than three or more times a day, and regimens with lower pill burdens are increasingly popular. Two drugs, didanosine and efavirenz , can be taken on a once daily regimen. Drugs with high pill burden such as amprenavir, nelfinavir and delavirdine will hopefully be improved with newer formulations which allow the same dose in fewer pills.

**Special Situations**

The initiation of HAART, once criteria for treatment are met, may not always be the best clinical decision. Specifically, in the setting of an active opportunistic infection with a life-threatening infection, therapy is usually delayed until the OI is resolved or controlled. This is generally an obvious approach. Not only does the immediate life-threatening problem take precedence over the long-range goals of HAART, but the critically ill patient is not in the optimal frame of mind for making decisions about HAART.

Another related situation is the patient with active tuberculosis. Rifampin, a cornerstone of most modern antituberculosis regimens, is a very potent inducer of P450 enzymes and interacts with all of the PIs and NNRTIs. The options include - delaying HAART until the completion of standard TB treatment; substituting rifabutin (at an adjusted dosage) for rifampin and using a regimen that does not contain nevirapine, delavirdine or saquinavir; or using a regimen with abacavir substituted for the PI or NNRTI arm of the regimen.

**Conclusion**

Today the patient has multiple good options, some more cumbersome, some with unique toxicity, but all with the potential to control their infection, restore immune function and prolong their life. The goals of therapy – suppression of viral replication to the lowest possible level and maintanence at the level – should not be surrendered to other factors. It makes no sense to administer a suboptimal regimen to enhance patient adherence. Patients objecting to a full HAART regimen need to an indepth review of the pathogenesis of HIV infection and the rational underlying therapy as we now understand it. If economics dictate a lesser regimen, then a delay in starting treatment might be a wiser course in hopes that alternative solutions (new economic support, drug study participation, or cheaper drugs) become available. The future will undoubtedly bring a drop in the costs as well as newer drugs.

**Suggested Reading**

Bartlett JG. Medical management of HIV infection. Port City Press, Baltimore 1999
(or on the web at www.hopkins-aids.edu

Carpenter CJ, Cooper DA, Fischl MA, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS Society – USA Panel. JAMA 2000;283:381-390.

DHHS Panel on Clinical Practices for Treatment of HIV Infection Guidelines for use of Antiretroviral Agents in HIV-infected Adults and Adolescents. http://www.hivatis.org.

Molina J-M, Chene G, Ferchal F, et al. The ALBI trial: a randomized controlled trial comparing stavudine plus didanosine with zidovudine plus lamivudine and a regimen alternating both combinations in previously untreated patients infected with human immunodeficiency virus. J Infect Dis 1999; 180:351-358.